IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Rajendra Narayanrao KANKAN et al

Attn: Applications

Serial No.: To be assigned

Filed: July 15, 2005

For: PHARMACEUTICAL PROCESS AND COMPOUNDS PREPARED THEREBY

CONFIRMATION OF CLAIM FOR PRIORITY

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

The benefit of the filing date of the following prior foreign application filed in the following foreign country is hereby requested for the above-identified application and the priority provided in 35 USC 119 is hereby claimed:

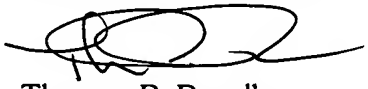
Indian Application No. 53/MUM/2003, filed January 15, 2003 and

Indian Application No. 193/MUM/2003, filed February 14, 2003.

A copy of the priority documents were filed in the International Stage (PCT).

It is requested that the file of this application be marked to indicate that the requirements of 35 USC 119 have been fulfilled and that the Patent and Trademark Office kindly acknowledge receipt of this document.

Respectfully submitted,



TPP/mat
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Date: July 15, 2005

15 JUL 2005

INTELLECTUAL
PROPERTY **INDIA**
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GEOGRAPHICALINDICATION

सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 15/01/2003 in respect of Patent Application No. 58/MUM/2003 of M/S. CIPLA LIMITED, 8, Bellasis Road, Mumbai Central, Mumbai-400 008, Maharashtra, INDIA, An Indian Company incorporated under the Companies Act 1956.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 14th day of May 2004.

(R. BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
[See section 7]

1. We,

   (a) M/S. CIPLA LIMITED

   (b) 8, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India

   (c) Indian company incorporated under the Companies Act 1956

2. Hereby declare –

   (a) that we are in possession of an invention titled **"IMPROVED PROCESS FOR PREPARING PROTON PUMP INHIBITORS"**

   (b) that the Complete Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

DUPLICATE

3. Further declare that the inventor(s) for the said invention are

   (a) Kankan, R. N.
   (b) A-3/5, N.B.D. Society, NSS Road, Ghatkopar, Mumbai – 400 084, Maharashtra, India
   (c) Indian National

   (a) Rao, D. R.
   (b) 4/403, Garden Enclave, Pokhran Road 2, Thane – 400 601, Maharashtra, India
   (c) Indian National

(a) **Srinivas, P.L.**
(b) 2475/24, 7th B Main, R.P.C. Layout, Vijaynagar, Bangalore – 560 040, Karnataka, India
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

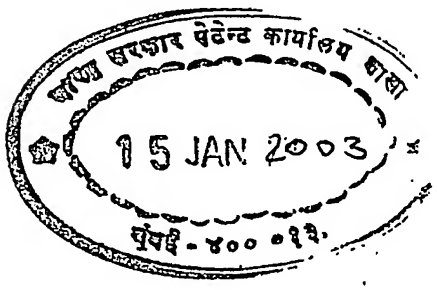
We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Kankan, Rajendra Narayanrao)

(Rao, Dharmaraj Ramachandra)

(Srinivas, Pathi Laxminarayan)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.



8. Following are the attachment with the application:
   (a) Provisional specification (3 copies)
   (b) Statement and Undertaking on Form 3
   (c) Form 26 [in original]
   (d) Fee Rs.5000/- in cheque bearing No.625551 dated 15th January 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

DR. GOPAKUMAR G. NAIR
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road
Kandivli (East), Mumbai – 400 101

To

The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
[See section 10]

"IMPROVED PROCESS FOR PREPARING PROTON PUMP INHIBITORS"

(a) **CIPLA LTD.**

(b) 8, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India

(c) Indian Company incorporated under the Companies Act 1956

DUPLICATE

The following specification describes the nature of the invention and the manner in which it is to be performed:

[0001] **IMPROVED PROCESS FOR PREPARING PROTON PUMP INHIBITORS**

[0002] **Field of the Invention**

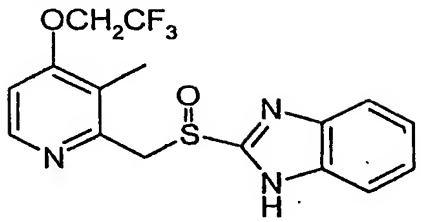
[0003] This invention in general relates to an improved process for preparation of proton pump inhibitors, more particularly the present disclosure relates to a simple and cost effective, eco-friendly and green chemistry process for oxidation of sulphides.

[0004] **Background of the Invention**

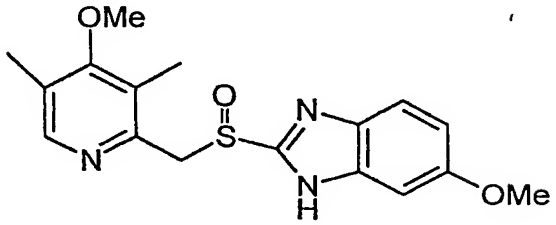
[0005] Proton Pump Inhibitors (PPIs) such as Lansoprazole, Omeprazole, Pantoprazole and Rabeprazole Sodium produce profound and sustained inhibition of gastric acid secretion. Responses of PPIs is more rapid than with other anti-secretory drugs. The PPIs work by completely blocking the production of stomach acid. They do this by inhibiting or shutting down a system in the stomach known as proton pump, the full name of which is "hydrogen-potassium adenosine triphosphate enzyme system". PPIs are the drug of choice in dyspepsia and peptic ulcers. In the treatment of peptic ulcers, the RRs of PPIs are superior to other drugs. PPIs are also drug of choice in Zollinger-Ellyson syndrome.

[0006] Lansoprazole is a well-known and widely used proton pump inhibitor. There are others like Omeprazole, Pantoprazole and Rabeprazole. The molecular and structural formula of the above compounds are given below:

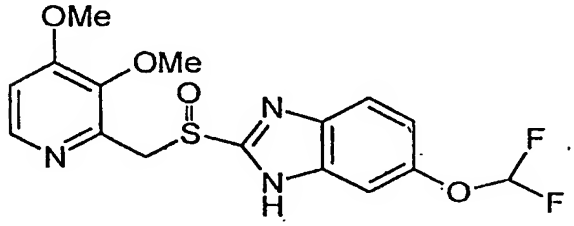
Lansoprazole



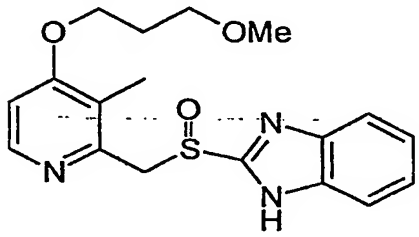
Omeprazole



Pantoprazole



Rabeprazole



The sulphinyl or sulphoxide group is common in all the above compounds. Since the present disclosure relates to a simple one step process for oxidation of the sulphide into the Sulphoxide (Sulphinyl) group to prepare the above

products, we will now refer to one of the above compounds viz. Lansoprazole as a representative compound of the proton pump inhibitors. However, the example of Lansoprazole is illustrative and the invention disclosed herewith is not limited to Lansoprazole, but applicable to the entire group of proton pump inhibitors.

[0007] Processes for the preparation of Lansoprazole are known. The prior art processes differ from each other in respect of different process chemistry followed.

[0008] Prior art processes addressed at the preparation of Lansoprazole involve the synthesis of the corresponding thioether compound, and its subsequent oxidation to the sulfinyl or sulfoxy compound, lansoprazole, by various methods such as reaction with hydrogen peroxide over a vanadium compound catalyst and reaction with peracids, peresters, ozone. There are several disadvantages associated with the known processes.

[0009] U. S. Patent No. 4,628,098 to Nohara, et al. discloses a process for preparation of Lansoprazole by oxidation of its sulphides using peracids (m-chloro perbenzoic acid).

[0010] U. S. Patent No. 5,840,552 to Holt, et al. discloses a process for preparation of Lansoprazole wherein sulphides are selectively bio-oxidised to isolate the pharmaceutically active enantiomer or enantiomerically enriched sulfoxide form, using microorganisms or microbial enzyme system.

[0011] U. S. Patent No. 5,374,730, to Slemon, et al discloses a process for the preparation of omeprazole and lansoprazole wherein amide analogues of the thioether compounds are readily oxidized to the corresponding sulfinyl compounds and the sulfinyl compounds are hydrolysed in alkaline medium to the corresponding carboxylic acid salts which can be decarboxylated to

omeprazole or lansoprazole, as the case may be. The disclosure refers to the advantages in relation to the purity in which the final products can be obtained, and the simplicity of the purification procedures. The amide compounds which are subjected to the oxidation step are crystalline solids, as opposed to oils, so that they are readily purified to a high degree of purity by relatively simply precipitation, crystallization and washing procedures. The carboxylates and carboxylic acid salts which are formed in the next synthetic step after oxidation are water soluble, whereas the final products, omeprazole and lansoprazole, are not. Accordingly, any unreacted residues of these compounds and many other minor impurities in the final products are simply removable by an aqueous washing procedure. Avoidance of significant discolouration of the product is the other advantage disclosed.

[0012] United States Patent No. 5,470,983 to Slemon, et al. titled 'Preparation of omeprazole and lansoprazole, and intermediates useful therein' discloses processes for producing Lansoprazole from acetamide-sulfide compounds by a process of oxidation to form the amide sulfinyl compound, followed by alkaline hydrolysis to the sulfinyl carboxylate or salt, and decarboxylation.

[0013] United States Patent No. 5,502,195, to Slemon, et al. is a Continuation-in-Part of application Ser. No. 276,378, which is in turn a division U.S. Pat. No. 5,374,730. This disclosure is addressed at a process for preparation of Lansoprazole, which is identical to the processes recited in issues Patent No.5, 470,983, wherein the acetamide sulphide is oxidized to amide sulfinyl compounds, which is then hydrolysed in alkaline medium to the carboxylic acid salts and then decarboxylated to form lansoprazole.

[0014] United States Patent No. 6,423,864 to Moon, et al. refers to the oxidation procedures employed in the prior art methods for converting a compound into lansoprazole as having problems in that many byproducts are formed and the yield of lansoprazole is low. EP Patent No. 134,400, GB Patent No. 2,134,523, U.S. Pat. No. 4,628,098, Korean Patent No. 52,837 discloses m-chloroperbenzoic acid as the oxidant. Spanish Patent Nos. 550,057, 540,147 and 539,793 disclose sodium periodate, iodosomethylbenzene and iodosobenzene, respectively, as the oxidant employed. These prior art processes have been cited to be unviable because of the expensive oxidants used therein which is also resulting in the production of many impurities and a low yield of the product in the range of about 60 to 80%.

[0015] A disadvantage in the prior art processes lies in the difficulty in purifying the title compound due to impurities resulting from over oxidation or partial oxidation of the thioether. This leads to complications in the processes for purifying the resultant lansoprazole.

[0016] Another disadvantage in the known process is the de-coloration of the title compound made by oxidation of the thioethers. Lansoprazole is an inherently unstable molecule in weakly acidic conditions, tending to rearrange to produce annoying highly coloured decomposition impurities. A red discolouration of the crude products is commonly experienced, and is very difficult to avoid, using this oxidation process.

[0017] A significant problem in the prior art processes is that they use highly hazardous/unsafe and unstable reagents like peracids (ex:- m-chloro perbenzoic acid) or difficult-to-access and handle microorganisms etc. The prior art processes are also cumbersome and involves catalyst (like vanadium).

[0018] Use of catalysts like vanadium leave behind in the final resultant product heavy metal residues and impurities, which are unacceptable and are difficult to remove totally. The purification processes for eliminating metallic impurities are costly and cumbersome. Additionally, catalysts are costly and needs careful preservation, storage as well as subject to regeneration or disposal concerns. With current concerns on solid waste disposals involving heavy metal wastes which are not environment friendly, a simple process not involving use of catalysts will not only be less costly but such a process will also involve less impurities in the final product, will avoid generation of unwanted, unwelcome solid (heavy metal) wastes, will be eco-friendly and will be classified as, most welcome, green chemistry in such a process could be of immense benefit not only on economic considerations but also on environment-friendly green chemistry reasons which are of immense importance in current world scenario.

[0019] It is therefore extremely important and essential to develop an industrially applicable and simple process of preparing the title compounds using simple non-hazardous reagent in aqueous solution not involving catalysts or hazardous peroxides, thereby addressing the deficiencies in the prior art processes.

[0020] Therefore there existed a need to devise an improved, simple, one-step process for producing Lansoprazole and other proton pump inhibitor using a readily and easily available economical reagent.

[0021] **Summary of Invention**

[0022] The present invention seeks to provide an simple and efficient method of oxidation of benzimidazole sulphides to the corresponding sulfinyl

compounds in high purity an d good yield using sodium hypochlorite as the oxidizing agent

[0023] Accordingly, we have sought to devise an improved process for oxidizing sulphides without employing catalysts. The improved process is addressed at preparing a Proton Pump Inhibitor (PPI), employing a preferred oxidizing agent at controlled temperature. The process is free from the deficiencies of the known art. The achievements of the objects of this invention will be made apparent in the description that follows.

[0024] Sodium hypochlorite is a mild oxidizing reagent used commonly in organic synthesis. The use of sodium hypochlorite has not been exemplified in prior art synthesis for oxidation of benzimidazole sulfides to sulfinyl compounds.

[0025] **Detailed Description of the Preferred Embodiments**

[0026] In one embodiment, the present invention discloses a process for producing Lansoprazole. The process comprises adding Lansoprazole sulphide to isopropyl alcohol at room temperature. The mixture is chilled to 0°C. Sodium hypochlorite is added slowly over a period of 2 hours and the temperature is maintained between 0-5°C. The temperature is maintained at the controlled levels as aforesaid for 5-6 hours. The reaction is monitored by TLC. Once the reaction is complete, the pH is adjusted to 7.0-7.5 using acetic acid at 5-10°C. The mixture is stirred for 30 mins at the same temperature conditions. The compound is then filtered, bed washed with water and suck dried.

[0027] In another embodiment the present invention discloses an improved process for producing Lansoprazole. The process comprises of purifying the resultant of process hereinabove described by dissolving it in 3

volumes methanol and 0.5 volumes of 10% sodium hydroxide solution at room temperature. The resultant is diluted with 1 ltr water. Activated charcoal is added and the mixture is stirred for 30 mins. It is then filtered over Hyflo, bed washed with 1 volume water. Adjust pH of the clear filtrate to 9.0-9.5 using 20% ammonium acetate solution at room temperature. After stirring for up to 30 minutes, the mixture is filtered, bed washed with 1 vol water and sucked dry. The material is dried at 40-45°C under vacuum and the resultant yield was found to be 60-65% w/w.

DATED THIS THE 15TH DAY OF JANUARY 2003

AGENT FOR THE APPLICANT

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